available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Clostridium difficile infections in patients with severe burns☆

Scott J. Crabtree [a], Janelle L. Robertson [a,b], Kevin K. Chung [c], Evan M. Renz [b,c], Steven E. Wolf [a,c,d], Duane R. Hospenthal [a,b,d], Clinton K. Murray [a,b,d,*]

[a] San Antonio Military Medical Center, Fort Sam Houston, TX, United States
[b] Uniformed Services University of the Health Sciences, Bethesda, MD, United States
[c] US Army Institute of Surgical Research, Fort Sam Houston, TX, United States
[d] University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

ARTICLE INFO

Article history:
Accepted 3 June 2010

Keywords:
Burn
Diarrhea
Clostridium difficile
Clostridial
Colitis

ABSTRACT

With improved survival in burn patients, *Clostridium difficile* infection (CDI) remains a significant potential complication. The incidence of, risk factors for, and outcomes of CDI in severely burned patients are poorly studied and remain unclear. This study involves retrospective case control and cohort studies using electronic medical records from February 1, 2002 to January 31, 2009 at the US Department of Defense's only burn unit. Demographic, risk factor, and outcome data were collected for all *C. difficile* toxin positive patients in the burn, medical, and surgical intensive care units and the hospital's step down unit along with an additional analysis of a 2:1 matched control of *C. difficile* toxin negative to positive burn patients. In the burn intensive care unit (BICU) population there was an incidence of 7.9 cases per 10,000 patient days; less than the non-burn unit rate of 15.2 cases (p-value < 0.01). The BICU patients were young males with a median 42% total body surface area burns. There were higher frequencies of operations and prior aminoglycoside use, with longer unit stays and times until death or discharge. There was no difference in treatments, morbidity, or mortality. The comparison of patients with positive and negative *C. difficile* toxin among those in the BICU revealed few significant differences in risk factors or outcomes. Differences in risk factors between burn and non-burn patients were likely markers of the populations rather than independent risk factors for CDI in the burn population with overall lower rates likely reflective of younger, healthier patients in the BICU and more aggressive infection control practices.

Published by Elsevier Ltd and ISBI

1. Introduction

Clostridium difficile (CD) diarrhea is a serious, infectious complication related to antibiotic exposure, which has been shown to prolong hospital stays and increase morbidity and mortality. *C. difficile* infection (CDI) in the intensive care unit (ICU) setting is particularly troublesome leading to an increase in attributable hospital mortality, prolonged ICU stay, and greater number of days in the hospital [1]. Exact incidence rates for CDI in the ICU setting have varied from 4.4 to 32 cases per 10,000 patient days [2–4]. Risk factors for CDI in the ICU do not differ significantly from commonly accepted risk factors identified in the general hospital setting: advanced age, prolonged hospitalization, severe underlying disease, concomitant infections, proton pump

☆ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the US Department of the Army, US Department of the Air Force, Department of Defense, or the US government. This work was prepared as part of their official duties and, as such, there is no copyright to be transferred.

* *Corresponding author at*: Infectious Disease Service, San Antonio Military Medical Center, Brooke Army Medical Center, 3851 Roger Brooke Drive, Fort Sam Houston, TX 78234, United States. Tel.: +1 210 916 8752; fax: +1 210 916 0388.
E-mail address: Clinton.Murray@amedd.army.mil (C.K. Murray).

0305-4179/$36.00. Published by Elsevier Ltd and ISBI
doi:10.1016/j.burns.2010.06.008

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 FEB 2011	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Clostridium difficile infections in patients with severe burns	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Crabtree S. J., Robertson J. L., Chung K. K., Renz E. M., Wolf S. E., Hospenthal D. R., Murray C. K.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**7**	

inhibitor use, recent gastrointestinal surgeries, enteral feeding tube placement, and antibiotic exposure [5,6]. Although cephalosporins, clindamycin, and broad-spectrum antibiotics have been implicated in the development of CDI, a wide range of antimicrobials have shown association with the disease whether as actual predisposing agents or simple markers for other established risk factors [7,8].

Burn patients are at high risk for infectious complications during their hospitalizations due to alterations in their skin and mucosal barriers, general altered physiology in response to the stress of injury, and increased incidence of established risk factors such as prolonged hospital stays, significant antibiotic exposure, frequent need for surgical intervention, and use of proton pump inhibitors. The only study to date on CDI conducted in a burn unit specifically was carried out in 1987 and had a limited number of patients yielding a prevalence of 7.65% [9]. With improvement in burn care since this time, extended survival in severely burned patients has allowed more time for infectious complications to occur [10]. It was with this in mind that we set out to further characterize the incidence, risk factors, and outcomes of CDI in severely burned patients admitted to the ICU.

2. Methods

Retrospective cohort and case control studies were undertaken utilizing an electronic medical records review of the Brooke Army Medical Center medical and surgical ICUs and step down unit in addition to the US Army Institute of Surgical Research (USAISR) Burn Center intensive care unit (BICU) from February 01, 2002 to January 31, 2009. BAMC is a 240-bed, verified Level 1 trauma center, serving both DoD beneficiaries and civilian emergency patients within the southern Texas region trauma system. BAMC operates 48 ICU bed designated for surgical, medical and cardiac intensive care patients. The 40-bed USAISR Burn Center within the BAMC facility includes a 16-bed BICU, and adjacent dedicated operating room suite. The surgical intensive care units (SICU) (2N and 2S) and medical intensive care units (MICU) (3S) are both semi-closed units caring for critically ill patients deemed in need of intensive care while the step down unit (3N) is typically composed of medical patients followed by general medicine staff requiring closer monitoring outside the intensive care unit setting. Standard care the burn center includes early excision and grafting and implementation of aggressive infection control to include strict contact precautions in individual rooms throughout the BICU admission. In all wards evaluated in this study, patients are admitted to single patient rooms with the implementation of contact precautions when patients develop diarrhea along with placards indicating that hand hygiene should involve soap and water. Periodic hand hygiene compliance surveys have indicated relatively consistent adherence across the various ICUs. Due to the fact that some SICU and MICU patients are housed in alternate units due to overflow and that our study is focused on investigating an infectious disease with close association to contact exposures it was decided to differentiate the non-burn ICUs by geographic location (2N, 2S, 3N, 3S) rather than patient type; care of burn patients is restricted to the BICU.

For the cohort study, all patients admitted to the BICU, non-burn ICUs, or step down units were screened with the electronic clinical microbiologic culture database for CD toxin screening in the stool. All patients identified with positive CD toxin assays were included in the study with the exception of patients with non-thermal burns who were excluded from the BICU cohort. CD toxin throughout the healthcare facility was obtained at the discretion of the clinician based upon the presence of fevers and/or elevated white blood cell count without a clear etiology along with the presence of diarrhea. Patients were then further evaluated by demographics (age and gender) and potential risk factors for CDI (time until positive, presence and duration of feeding tubes, mechanical ventilation, number of total and GI surgeries, and proton pump inhibitor (PPI) and prior antibiotic exposure). The patient's clinical condition on day of positive CD toxin assay was evaluated using the systemic inflammatory response syndrome (SIRS) and burn sepsis criteria as detailed American College of Chest Physicians/Society of Critical Care Medicine and American Burn Association Consensus Conferences, respectively [13,14]. Treatments and outcomes were recorded to include antibiotic choice, incidence of toxic colitis, length of unit stay and time to death or discharge, and any cases of in-hospital mortality. Prior antibiotic use was defined as the receipt of any antibiotics inpatient or outpatient within 60 days prior to positive toxin assay. To further simplify management of antibiotic data, each agent was classified into one of six groups consisting of cephalosporins, fluoroquinolones, parenteral vancomycin, aminoglycosides, penicillin derivatives (non-cephalosporin beta-lactams), and a final group to include all others. PPI use was identified if given within 60 days prior to positive toxin assay.

For the case control study, a 1:2 matched positive to negative CD toxin results for BICU patients were matched by time of admission (±19 months), age (±15 years), gender, and TBSA (±15%). Charts were evaluated via the methods outlined in the cohort study with additional burn characteristics data (% total body surface area (TBSA), full thickness burns, and the presence of inhalation injury).

Statistical analyses were performed using the statistical software SPSS. Descriptive frequencies were expressed using medians with ranges provided. When comparing CDI positive burn patients with CDI negative burn patients, these patients were matched in a 2:1 fashion by gender, age and %TBSA. Continuous data was evaluated using a repeated measures ANOVA while nominal and ordinal data was evaluated by the Friedman test. CDI positive burn patients were compared with patients in multiple other (non-burn) intensive care units. These patients were not matched. For non-normally distributed data that was continuous, the differences between populations were evaluated with the Mann–Whitney *U* test. For categorical data comparisons, the chi-square test was used. No variable was normally distributed. Incidence rates were calculated by dividing total cases of CDI in each unit by total number of patient bed days for each unit. Due to limitations in hospital bed day data, only the study periods after January 01, 2004 were included in the bed day analysis. In addition, rates were determined by number of patients with tests for CDI by the number with positive tests.

3. Results

During the study period, 14 patients developed CDI while hospitalized in the BICU among the 180 tested. Thirteen of these patients developed CDI in the time period we have total admissions data for, as there was insufficient records from 2002 to 2003, revealing an infection rate of 7.9 cases per 10,000 patient days (Table 1). Among the non-burn ICUs, there were 11, 16, 18, and 28 cases among the 77, 97, 93, and 169 tested in 3N, 2S, 2N, and 3S, respectively. The overall rates for these

Table 1 – Incidence rates of *Clostridium difficile* diarrhea for each unit by number tested and patient bed days.[a].

	Cases of CDI	Number of patients tested	Number of patient days	Cases of CDI per patient tested	Cases of CDI per 10,000 patient days[c]
BICU					
2002	1	14		0.07	
2003	0	23		0.00	
2004	3	25	2005	0.12	15.0
2005	6	31	3841	0.19	15.6
2006	4	36	3754	0.11	10.7
2007	0	30	3401	0.00	0.0
2008	0	21	3358	0.00	0.0
2009[b]	0	0		0.00	
Total	14	180	16,359	0.08	7.9
3N					
2002	6	13		0.46	
2003	5	15		0.33	
2004	2	20	2694	0.10	7.4
2005	4	15	2866	0.27	14.0
2006	2	13	2697	0.15	7.4
2007	0	13	2657	0.00	0.0
2008	3	16	2780	0.19	10.8
2009[b]	0	0		0.00	
Total	22	105	13,694	0.21	8.0
3S					
2002	3	26		0.12	
2003	5	36		0.14	
2004	9	37	2345	0.24	38.4
2005	5	44	2645	0.11	18.9
2006	8	29	2455	0.28	32.3
2007	4	33	2401	0.12	16.7
2008	2	26	2316	0.08	8.6
2009[b]	0	0		0.00	
Total	36	231	12,162	0.16	23.0
2N					
2002	4	9		0.44	
2003	3	17		0.18	
2004	2	21	2217	0.10	9.0
2005	9	14	2351	0.64	38.3
2006	2	16	2331	0.12	8.6
2007	3	24	2265	0.12	13.2
2008	2	18	1897	0.11	10.5
2009[b]	0	0		0.00	
Total	25	119	11,061	0.21	16.3
2S					
2002	2	24		0.08	
2003	1	23		0.04	
2004	4	20	2167	0.20	18.5
2005	2	20	2543	0.10	7.9
2006	6	16	2379	0.38	25.2
2007	2	24	2115	0.08	9.5
2008	2	17	1967	0.12	10.2
2009[b]	0	0		0.00	
Total	19	144	11,171	0.13	14.3

[a] Incidence data is only for patients admitted after January 1, 2004.
[b] Data through 1 January 2009, so no rates provided.
[c] Patient days are for all admissions to the unit.

non-burn ICUs were generally higher at 8.0, 14.3, 16.3, and 23.0 cases per 10,000 patient days in 3N, 2S, 2N, and 3S, respectively. Overall, the BICU infection rate was significantly lower than the combined non-burn ICU and step down unit average of 15.2 cases per 10,000 patient days.

3.1. *Characteristics, interventions, and outcomes in cohort study*

The median age of the CDI positive BICU patients was 25.5 (range 19–72) and 92.2% were male while in the non-burn ICUs and step down unit the median ages of CDI positive patients were significantly older (median 70, range 19–94) with a smaller proportion of males (58.4%) (Table 2).

CDI positive BICU patients tended to have longer unit stays (median 26.0 days, range 4–98) relative to CDI positive patients in the non-burn ICUs and step down unit (median 13.0 days, range 1–154) (p-value <0.01). CDI positive BICU patients also underwent significantly more surgical procedures (median 2.0 [range 0–18] vs. 0.0 [range 0–18], p-value <0.01) though there was a high degree of variability with this depending on whether the patient was cared for by a SICU or MICU team (see Table 2). Antibiotic treatment prior to the diagnosis of CDI was similar across most units though BICU patients received greatly increased amounts of aminoglycosides (78.6% vs. 20.8%, p-value <0.01) and slightly less cephalosporins (14.3% vs. 49.5%, p-value 0.013). Clinically BICU patients positive for CDI had greater body temperatures at time of diagnosis with

Table 2 – Characteristics of *Clostridium difficile* confirmed diarrhea patients in all intensive care units.

	BICU (N = 14)	2N (N = 25)	2S (N = 19)	3N (N = 21)	3S (N = 36)	All ICU except BICU (N = 101)	p-Values for BICU vs. all other ICUs
Age (range)	25.5 (19–72)	73.0 (20–91)	68.0 (25–87)	58.0 (19–94)	68.5 (37–88)	70.0 (19–94)	<0.01
Male gender (%)	13 (92.9%)	19 (76%)	8 (42.1%)	10 (47.6%)	22 (61.1%)	59 (58.4%)	0.016
Days in unit (range)	26.0 (4–98)	15.0 (2–58)	26.0 (2–154)	23.0 (2–42)	8.5 (1–28)	13.0 (1–154)	0.018
Days on ventilator (range)	0 (0–41)	3.0 (0–50)	3.0 (0–39)	0 (0–29)	0 (0–46)	0 (0–50)	0.549
# of surgeries (range)	2.0 (0–18)	1.0 (0–18)	1.5 (0–10)	1.0 (0–9)	0 (0–2)	0 (0–18)	<0.01
# of gastrointestinal surgeries (range)	0 (0–1)	0 (0–8)	0 (0–2)	0 (0–3)	0 (0)	0 (0–8)	0.508
Antibiotics in past 60 days							
Cephalosporins	2 (14.3%)	14 (56.0%)	9 (47.4%)	8 (38.1%)	19 (52.8%)	50 (49.5%)	
Fluoroquinolones	7 (50%)	16 (64.0%)	13 (68.4%)	10 (47.6%)	27 (75.0%)	66 (53.0%)	0.013
Vancomycin	11 (78.6%)	18 (72.0%)	11 (57.9%)	11 (52.4%)	22 (61.1%)	62 (61.4%)	–
Aminoglycosides	11 (78.6%)	9 (36.0%)	3 (15.8%)	5 (23.8%)	4 (11.1%)	21 (20.8%)	–
Penicillin derivatives	9 (64.3%)	19 (76.0%)	15 (78.9%)	13 (61.9%)	24 (66.7%)	71 (70.3%)	<0.01
Other	3 (21.4%)	9 (36.0%)	8 (42.1%)	8 (38.1%)	14 (38.9%)	39 (38.6%)	–
Proton pump inhibitor use (%)	14 (100%)	22 (88%)	18 (94.7%)	15 (71.4%)	29 (80.6%)	82 (82%)	0.121
Days from admit to diagnosis (range)	10 (1–92)	11 (0–59)	17 (0–41)	5 (0–32)	3.5 (0–27)	7 (0–59)	0.091
SIRS-temperature[a] (%)	12 (85.7%)	9 (36.0%)	10 (52.6%)	10 (47.6%)	12 (33.3%)	41 (41%)	<0.01
SIRS-respiratory rate	10 (71.4%)	21 (84%)	17 (17%)	18 (85.7%)	32 (88.9%)	88 (87.1%)	0.219
SIRS-heart rate	12 (85.7%)	21 (84%)	14 (73.3%)	18 (85.7%)	26 (72.2%)	79 (78.2%)	0.731
SIRS-white blood cell count	10 (71.4%)	15 (60%)	12 (63.2%)	18 (85.7%)	21 (58.3%)	62 (61.3%)	0.467
Sepsis (%)	12 (85.7%)	22 (88%)	16 (84.2%)	20 (38.1%)	32 (88.9%)	90 (89.1%)	0.658
Treatment (%)							
Nothing	1 (7.1%)	1 (4.0%)	0	0	3 (8.3%)	4 (4.0%)	0.695
Metronidazole (IV)	12 (85.7%)	18 (72.0%)	15 (78.9%)	17 (81.0%)	28 (77.8%)	78 (77.2%)	
Vancomycin (PO)	0	2 (8.0%)	0	0	1 (2.8%)	3 (3.0%)	
Both	1 (7.1%)	4 (16.0%)	4 (21.2%)	4 (19.0%)	4 (11.1%)	16 (15.8%)	
Morbidity (%)							
Colectomy	0	1 (4.0%)	2 (10.5%)	1 (4.8%)	1 (2.8%)	5 (5.0%)	0.597
Toxic colitis	0	0	1 (5.3%)	0	1 (2.8%)	2 (2.0%)	
Mortality (%)	4 (28.6%)	7 (28%)	6 (31.6%)	0	12 (33.3%)	25 (24.8%)	0.749
Attributable mortality (% of deaths)	0	1 (14%)	3 (50%)	0	5 (42%)	9 (36%)	0.273
Days to death or discharge (range)	43 (6–152)	15 (2–79)	21 (2–212)	10 (1–60)	7 (0–53)	11 (0–212)	<0.01

[a] SIRS-temperature: <36 °C or >38 °C; SIRS-respiratory rate: >20 breaths/min or P_{CO_2} < 32 mm Hg; SIRS-heart rate: >90 beats/min; SIRS-white blood count: <4000 cells/mm^3 or >12,000 cells/mm^3 or >10% band forms. All as defined by 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.

85.7% meetings SIRS criteria for temperature versus 41% of CDI positive patients in the non-burn ICUs and step down unit (p-value <0.01). This was the only one of the four SIRS criteria that was significantly different, however, and overall there was no statistically significant difference in the incidence of sepsis in BICU patients versus patients in the other units.

CDI positive patients in the BICU had significantly longer times till death or discharge (median 43 days, range 6–152) relative to CDI positive patients in the non-burn ICUs and the step down unit (median 11 days, range 0–212) (p-value <0.01). There was no significant difference in the treatment, morbidity, or mortality of CDI positive patients in all populations studied (see Table 3). Although no further treatment was rendered in burns while 5 of 101 in the other groups underwent colectomy or developed toxic colitis. The majority of patients received parenteral metronidazole in all units (range 72.0–85.7%) with the remainder typically receiving both parenteral metronidazole and oral vancomycin (range 7.1–21.2%). There was no difference in the incidence of toxic colitis or need for colectomy and mortality was 28.6% in the BICU compared to 24.8% in all other intensive care and step down units (p-value 0.749). There was no attributable mortality in the BICU, however, and attributable mortality was variable in the other ICUs (range 14.3–50.0% of deaths) though none of this was statistically significant.

3.2. *Characteristics and outcomes in case control study*

The median age of the CDI negative BICU patients was 29 (range 20–72) and 92.9% were male as matched (Table 3). With regards to their burns, the median TBSA was 43% (range 1–77.5%) as matched and there was no significant difference in the incidence of full thickness burns or inhalation injury. Relative to the CDI positive burn patients, the CDI negative burn patients underwent more surgeries (median 4.0 [range 0–14] vs. 2.0 [range 0–18], p-value 0.019) and on average stayed longer in the BICU (median 38.0 days [range 9–228] vs. 26.0 days [range 4–98], p-value <0.01). With regards to antibiotic therapy

Table 3 – Characteristics of burned patients with and without *Clostridium difficile* confirmed diarrhea.

	C. difficile positive (N = 14)	*C. difficile* negative (N = 28)	p-Value
Age (range)	25 (19–72)	29 (20–72)	Matching criteria
Male gender (%)	13 (92.2%)	26 (92.9%)	Matching criteria
TBSA (%)	42 (±25)	43 (±23)	Matching criteria
Full thickness burn (%)	12 (85.7%)	25 (89.3%)	0.607
Inhalation injury (%)	7 (50.0%)	12 (42.9%)	0.670
Days in unit (range)	26.0 (4–98)	38.0 (4–228)	<0.01
Days on ventilator (range)	0.0 (0–41)	0.0 (0–92)	<0.01
# of surgeries (range)	2 (0–18)	4 (0–14)	0.019
# of gastrointestinal surgeries (range)	0 (0–1)	0 (0–2)	0.735
Antibiotics in past 60 days (%)			
Cephalosporins	2 (14.3%)	4 (14.3%)	
Fluoroquinolones	7 (50%)	11 (39.3%)	0.05
Parenteral vancomycin	11 (78.6%)	26 (92.9%)	
Aminoglycosides	11 (78.6%)	28 (100%)	
Penicillin derivatives	9 (64.3%)	23 (82.1%)	
Other	3 (21.4%)	10 (35.7%)	
Proton pump inhibitor use (%)	14 (100%)	28 (100%)	1.0
Days from admit to diagnosis (range)	10 (1–92)	N/A	
SIRS-temperature[a] (%)	12 (85.7%)	24 (85.7%)	0.549
SIRS-respiratory rate	10 (71.4%)	24 (85.7%)	0.449
SIRS-heart rate	12 (85.7%)	28 (100%)	0.135
SIRS-white blood cell count	10 (71.4%)	18 (64.3%)	0.895
Sepsis (%)	12 (85.7%)	27 (96.4%)	0.368
Treatment (%)			
Nothing	1 (7.1%)		
Metronidazole (IV)	12 (85.7%)		
Vancomycin (PO)	0		
Both	1 (7.1%)		
Morbidity (%)			
Colectomy	0		
Toxic colitis	0		
Mortality (%)	4 (28.5%)	12 (42.9%)	0.641
Attributable mortality (% of deaths)	0		
Days to death or discharge (range)	43.0 (6–152)	26.5 (1–112)	<0.01

[a] Systemic inflammatory response system (SIRS)-temperature: <36 °C or >38 °C; SIRS-respiratory rate: >20 breaths/min or P_{CO_2} < 32 mm Hg; SIRS-heart rate: >90 beats/min; SIRS-white blood count: <4000 cells/mm^3 or >12,000 cells/mm^3 or >10% band forms. All as defined by 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.

prior to testing for CDI, the CDI negative patients received aminoglycoside antibiotics in greater frequency than the CDI positive patients (100% vs. 78.6%, p-value 0.05) with no other significant differences in therapy. The time to death or discharge from the hospital after time of testing was significantly shorter for the CDI negative burn patients at 26.5 days (range 1–112, p-value <0.01). Twelve (42.9%) of the 28 CDI negative BICU patients died (vs. 28.6% of the 14 CDI positive BICU patients) during their admission though this mortality difference was not significant (p-value 0.641).

4. Discussion

C. difficile infection continues to remain an important problem and perennial complication of hospitalization but appears less so in BICU patients versus patients admitted to other ICUs. With its association with significant morbidity and mortality and its potentially preventable nature, attention must be paid to its various risk factors and general evolution over time. Advances in burn care, including early excision and grafting, have yielded improved survival over the past 30 years thus compelling greater attention to hospital associated complications [15,16].

Although methods of reporting have varied, CDI rates in the ICU in general have fluxed in recent studies with the Centers for Disease Control and Prevention reporting 5.0 cases per 10,000 patient days from 1987 to 2001 in the National Healthcare Safety Network (known previously as the NNISS) and rates of 32.0 cases per 10,000 patient days from 1997 to 1999 in the ICU of a Midwestern tertiary care referral center [4,5]. Results from our study show rates in the non-burn and step down unit setting within this range at 15.2 cases per 10,000 patient days. Interestingly, although rates in our BICU are higher than the national rate reported by the NNISS, at 7.9 cases per 10,000 patient days they are significantly below our medical and surgical ICU average. The reason for this difference is not readily clear though it is likely related to both the rigorous infection control procedures practices in the BICU implemented for all admitted burn patients and the relatively young and healthy composition of most our burn population, two factors known for decreased incidence of the disease [7,8].

There was no clear difference in risk factors for the acquisition of CDI either in comparing positive and negative burn patients to one another or in comparing positive burn patients to positive patients in the other intensive care and step down units. Established risk factors such as number of days in the ICU setting, number of feeding tubes and operations, and specific antibiotic administration were either not significant in our study or in fact counter to the previously identified norm in that CDI negative patients tended to have more surgeries, more feeding tubes, and longer lengths of stay in the BICU. Similarly, though CDI positive burn patients had significantly more surgeries and time spent in the ICU compared to their non-burn CDI positive patients, it is likely this is simply representative of the burn population in general as evidenced by similar figures in the CDI negative burn patients and thus not an indication of an independent risk factor for the development of CDI in burn patients. Antibiotic data revealed increased aminoglycoside use in all BICU patients relative to patients admitted to the other intensive care and step down units with the greatest use in CDI negative BICU patients. With such a trend, it is unclear if these statistically significant differences are an indication of protective benefit of the antibiotics, absence of detrimental effect of the aminoglycosides relative to other antibiotics, or some other unknown process. There is no literature to date to suggest a protective benefit of the drug class except possibly when given as an alternative to another antibiotic regimen [12].

Treatment in the vast majority of cases was most often intravenous metronidazole as is consistent with previously established SHEA and IDSA guidelines [11]. Although there were cases of patients receiving either oral vancomycin alone or in combination with metronidazole, these differences were not significant. Morbidity was low with increased hospital stays for CDI positive burn patients relative to CDI negative burn patients, but there were no cases of toxic colitis requiring colectomy in either population. Both mortality and attributable mortality were variable from unit to unit, but these differences were not significant. Overall rates of attributable mortality in the intensive care and step down unit setting were higher than prior studies at 36% of deaths with previously recorded values ranging from 4.87 to 6.1%, though definitions of attributable mortality were variable in the literature. There was, however, no attributable mortality among the BICU patients [1,2].

It is clear that CDI continues to trouble our ICUs and continues to remain a significant source of morbidity and mortality. Although there were no cases requiring colectomy and no attributable mortality in the BICU, it is likely that this is due to the small sample size of our population and that our study is simply underpowered as evidenced by the prevalence of both of these in the larger sized general ICU sample. Study results are similarly limited by the significant population differences and retrospective nature of our study. The electronic medical record provided by the Department of Defense is quite robust, but nevertheless there was inconsistent record of antibiotic administration during transportation back from the theater of war for many of the CDI positive and negative burn patients injured in recent combat operations. In addition, it was difficult to differentiate clearly from CD infection versus carrier state, but the CD toxins were obtained when patients presented with a clinical syndrome consistent with possibly CDI. Finally, it was challenging to compare disease severity across the various wards in the study because different disease severity scores are not applicable to all patient populations in this study. With this in mind, further studies with a better monitored and more representative demographic are needed.

The fact remains despite aggressive infection control measures in the BICU and relative health of most patients admitted to it, CDI remains prevalent in the severely burned population though at a low absolute rate of cases with very limited attributable mortality. Those who do develop it have more operations and longer length of stay, and have more aminoglycoside use. Development of *C. difficile* colitis in the BICU is not typically associated with toxic megacolon or other complications, however, the sample size is relatively small, and cannot be reliably compared to the approximately 5%

incidence in other institutional ICUs. Although less suspicion for CDI in BICU patients because of their demographics is perhaps indicated as evidenced by the decreased incidence, it should continue to be on the differential in a severely injured population that regularly receives large amounts of antibiotics and routinely requires prolonged hospitalizations. Until further studies can be conducted in a larger, multi-center approach to fully elucidate risks and outcomes of CDI in the BICU, continued vigilance is warranted in this at risk population.

Conflict of interest

The authors have no conflicts of interest to report.

REFERENCES

[1] Kennealley C, Rosini JM, Skrupky LP, Doherty JA, Hollands JM, Martinez E, et al. Analysis of 30-day mortality for *Clostridium difficile*-associated diseases in the ICU setting. Chest 2007;132:418–24.

[2] Ang CW, Heyes G, Morrison P, Carr B. The acquisition and outcome of ICU-acquired *Clostridium difficile* infection in a single centre in the UK. J Infect 2008;57:435–40.

[3] Rotimi VO, Mokaddas EM, Jamal WY, Verghese TL, el-Din K, Junaid TA. Hospital acquired *Clostridium difficile* infection amongst ICU and burn patients in Kuwait. Med Princ Pract 2002;11:23–8.

[4] Archibald LK, Banerjee SN, Jarvis WR. Secular trends in hospital acquired *Clostridium difficile* disease in the United States, 1987–2001. J Infect Dis 2004;189:1585–9.

[5] Lawrence S, Puzniak L, Shadel B, Gillespie KN, Kollef MH, Mundy LM. *Clostridium difficile* in the intensive care unit: epidemiology, costs, and colonization pressure. Infect Control Hosp Epidemiol 2007;28:123–30.

[6] Marcon AP, Gamba MA, Vianna LA. Nosocomial diarrhea in the intensive care unit. Brazil J Infect Dis 2006;10(6): 384–9.

[7] Marra AR, Edmond MB, Wenzel RP, Bearman GM. Hospital acquired *Clostridium difficile*-associated disease in the intensive care unit setting: epidemiology, clinical course, and outcome. BMC Infect Dis 2007;7:42–8.

[8] Howitt JR, Grace JW, Schaefer MG, Dolder C, Cannella C, Schaefer RS. *Clostridium difficile*-positive stools: a retrospective identification of risk factors. Am J Infect Control 2008;36:488–91.

[9] Grube BJ, Heimbach DM, Marvin JA. *Clostridium difficile* diarrhea in critically ill burned patients. Arch Surg 1987;122:655–61.

[10] Church D, Elsayed S, Reid O, Lindsay R. Burn wound infections. Clin Microbiol Rev 2006;19:403–34.

[11] Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva Jr J. *Clostridium difficile* associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995;16:459–77.

[12] Starks I, Ayub G, Walley G, Orendi J, Roberts P, Maffulli N. Single-dose cefuroxime with gentamicin reduces *Clostridium difficile*-associated disease in hip fracture patients. J Hosp Infect 2008;70:21–6.

[13] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644–55.

[14] Greenhalgh DG, Saffle JR, Holmes 4th JH, Gamelli RL, Palmieri TL, Horton JW, et al. American Burn Association Consensus Conference to define sepsis and infection in burns. J Burn Care Res 2007;28:776–90.

[15] Palmieri TL. What's new in critical care of the burn-injured patient? Clin Plast Surg 2009;36:607–15.

[16] White CE, Renz EM. Advances in surgical care: management of severe burn injury. Crit Care Med 2008;36:S318–24.